

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Coronary Drug-Eluting Stent
Device Trade Name:	SYNERGY™ XD Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™)
	SYNERGY MEGATRON™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™)
	SYNERGY™ SHIELD Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™)
Device Prococode:	NIQ
Applicant's Name and Address:	Boston Scientific Corporation 300 Boston Scientific Way Marlborough, MA 01752-1566
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P150003/S105
Date of FDA Notice of Approval:	January 27, 2025

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail and Over-the-Wire) PMA (P150003) was originally approved on July 30, 2016. The SYNERGY family of stents approved under that PMA and various supplements are indicated for improving luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease, stable angina, unstable angina, non-ST elevation MI or documented silent ischemia due to atherosclerotic lesions in native coronary arteries ≥ 2.25 mm to ≤ 5.00 mm in diameter in lesions ≤ 44 mm in length and for high bleeding risk patients with coronary arteries ≥ 2.25 mm to ≤ 5.00 mm in diameter in lesions ≤ 34 mm in length. The SSEDs to support these indications are available on the following CDRH websites and are incorporated into the current SSED by reference here.

-P150003: http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150003B.pdf
-P150003/S003: http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150003S003B.pdf
-P150003/S058: http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150003S058B.pdf

The current supplement was submitted to expand the indication for the SYNERGY, SYNERGY XD, SYNERGY MEGATRON, and SYNERGY SHIELD Everolimus-Eluting Platinum Chromium Coronary Stent Systems to include patients with ST segment-elevation MI (STEMI).

II. INDICATIONS FOR USE

Note that the indications for each stent in the SYNERGY family of stents vary regarding vessel and lesion size. The indications approved in this supplement for the SYNERGY XD, SYNERGY MEGATRON, and SYNERGY SHIELD are listed below.

The SYNERGY™ XD Everolimus-Eluting Platinum Chromium Coronary Stent System is indicated for improving luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease, stable angina, unstable angina, ST-elevation MI (STEMI), non-ST elevation MI or documented silent ischemia due to atherosclerotic lesions in native coronary arteries ≥ 2.25 mm to ≤ 5.00 mm in diameter in lesions ≤ 44 mm in length and for high bleeding risk patients with coronary arteries ≥ 2.25 mm to ≤ 5.00 mm in diameter in lesions ≤ 34 mm in length.

The SYNERGY™ MEGATRON Everolimus-Eluting Platinum Chromium Coronary Stent System is indicated for improving luminal diameter in patients, including those at high risk for bleeding, with diabetes mellitus, with symptomatic heart disease, stable angina, unstable angina, ST elevation MI, non-ST elevation MI or documented silent ischemia due to atherosclerotic lesions in native coronary arteries ≥ 3.50 mm to ≤ 5.00 mm in diameter in lesions ≤ 28 mm in length.

The SYNERGY™ SHIELD Everolimus-Eluting Platinum Chromium Coronary Stent System is indicated for improving luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease, stable angina, unstable angina, ST elevation MI, non-ST elevation MI or documented silent ischemia due to atherosclerotic lesions in native coronary arteries ≥ 2.25 mm to ≤ 5.00 mm in diameter in lesions ≤ 44 mm in length and for high bleeding risk patients with coronary arteries ≥ 2.25 mm to ≤ 5.00 mm in diameter in lesions ≤ 34 mm in length.

III. CONTRAINDICATIONS

Use of the SYNERGY™, SYNERGY™ XD, SYNERGY™ MEGATRON, and SYNERGY™ SHIELD Everolimus-Eluting Platinum Chromium Coronary Stent System is contraindicated in patients with known hypersensitivity to:

- 316L stainless steel, platinum, chromium, iron, nickel or molybdenum;
- Everolimus or structurally-related compounds; and/or
- The polymer or their individual components.

Coronary Artery Stenting is contraindicated for use in:

- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.
- Patients with uncorrected bleeding disorders or patients who cannot receive anticoagulation or antiplatelet aggregation therapy.

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System, SYNERGY™ XD Everolimus-Eluting Platinum Chromium Coronary Stent System, SYNERGY™ MEGATRON Everolimus-Eluting Platinum Chromium Coronary Stent System, and SYNERGY™ SHIELD Everolimus-Eluting Platinum Chromium Coronary Stent System respective labeling.

V. **DEVICE DESCRIPTION**

The SYNERGY family of stents are device/drug combination products that provide a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. Both systems consist of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) delivery catheter. SYNERGY can also be mounted as an Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY™, SYNERGY™ XD, SYNERGY™ MEGATRON, and SYNERGY™ SHIELD Everolimus-Eluting Platinum Chromium Coronary Stent Systems (hereafter referred to as SYNERGY, SYNERGY XD, SYNERGY MEGATRON, and SYNERGY SHIELD, SYNERGY family of stents, or SYNERGY are described in Table 1.

Table 1: SYNERGY Family of Stents Product Description

	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System	SYNERGY XD/ SHIELD Monorail Stent Delivery System	SYNERGY MEGATRON Monorail Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38		8, 12, 16, 20, 24, 28, 32, 38, 48*	8, 12, 16, 20, 24, 28, 32
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50**, 5.00**	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50** and 5.00**	3.50, 4.00, 4.50 and 5.00
Stent Material	Platinum Chromium Alloy (PtCr)			

Stent Strut Thickness	2.25 mm to 2.75 mm: 0.0029 inches (0.074 mm) 3.00 mm to 3.50 mm: 0.0031 inches (0.079 mm) 4.00 mm to 5.00 mm: 0.0032 inches (0.081 mm)	2.25 mm to 2.75 mm: 0.0029 inches (0.074 mm) 3.00 mm to 3.50 mm: 0.0031 inches (0.079 mm) 4.00 mm to 5.00 mm: 0.0032 inches (0.081 mm)	0.0035 inches (.089 mm)
Drug Product	An abluminal (outer surface of the stent in contact with the vessel wall) coating of a polymer carrier with approximately 1 µg of everolimus per mm ² of total stent surface area with a maximum nominal drug content of 287 µg on the largest stent (38 mm) for SYNERGY, 364 µg on the largest stent for XD/SHIELD (48 mm), and 237.4 µg on the largest stent for MEGATRON 32 mm).		

	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System	SYNERGY XD/SHIELD Monorail Stent Delivery System	SYNERGY MEGATRON Monorail Stent Delivery System
Delivery System				
Effective Length	144 cm			
Delivery System Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤ 0.014 inches (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤ 0.014 inches (0.36 mm)	Single access port to inflation lumen. Guidewire exit port is located approximately 23 cm (XD) and 26 cm (SHIELD) from tip. Designed for guidewire ≤ 0.014 inches (0.36 mm)	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤ 0.014 inches (0.36 mm).
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.4 mm (0.016 inches) beyond the stent at each end.			
Balloon Inflation Pressure	Nominal Inflation Pressure for all the diameters: 11 atm (1117 kPa)			
	Rated Burst Inflation Pressure: <ul style="list-style-type: none"> Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) Diameters 3.00 mm – 5.00 mm: 16 atm (1620 kPa) 	Rated Burst Inflation Pressure: <ul style="list-style-type: none"> Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) Diameters 3.00 mm – 4.00 mm: 16 atm (1620 kPa) 	Rated Burst Inflation Pressure: <ul style="list-style-type: none"> Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) Diameters 3.00 mm – 5.00 mm: 16 atm (1620 kPa) 	Rated Burst Inflation Pressure: <ul style="list-style-type: none"> Diameters 3.50 – 5.00 mm: 16 atm (1620 kPa)
Catheter Shaft Outer Diameter	Proximal: 2.1 F (0.70 mm) Distal: 2.25 mm – 2.75 mm: 2.6F (0.90 mm) 3.00 mm: <ul style="list-style-type: none"> (8 – 28 mm): 2.6F (0.90 mm) (32 – 38 mm): 	Proximal: 3.2F (1.07 mm) for 2.25 to 3.50 mm sizes, 3.4F (1.15 mm) proximal for 4.00 mm sizes Distal: 2.4F (0.82 mm) for 2.25 to 2.75 mm sizes, 2.7F (0.92 mm) for 3.00 to 4.00 mm sizes	XD - Proximal: 2.0 F (0.67 mm) SHIELD - Proximal: 2.1F (0.70 mm) Distal: 2.25 mm – 2.75 mm: 2.6F (0.89 mm) 3.00 mm: <ul style="list-style-type: none"> (8 – 28 mm): 2.6F 	Proximal: 2.1F (0.70 mm) Distal: 3.50 mm: <ul style="list-style-type: none"> 8 mm – 20 mm: 2.6F (0.89 mm) 24 mm – 32 mm: 2.7F (0.92 mm) 4.00 mm - 5.00 mm: 8mm – 32 mm: 2.7F

	2.7F (0.95 mm) 3.50 mm: • (8 – 20 mm): 2.6F (0.90 mm) • (24 – 38 mm): 2.7F (0.95 mm) 4.00 mm – 5.00 mm: 2.7F (0.95 mm)		(0.89 mm) • (32 – 48 mm): 2.7F (0.92 mm) 3.50 mm: • (8 – 20 mm): 2.6F (0.89 mm) • (24 – 48 mm): 2.7F (0.92 mm) 4.00 mm – 5.00 mm: 2.7F (0.92 mm)	(0.92 mm)
Guide Catheter Minimum Inner Diameter Requirement	2.25 – 4.00 mm: ≥ 5F (0.056 inches/1.42 mm) 4.50 mm – 5.00 mm: ≥ 6F (0.066 inches/1.68 mm)	≥6F (0.066 inches/1.68 mm)	2.25 – 4.00 mm: ≥ 5F (0.056 inches/1.42 mm) 4.50 mm – 5.00 mm: ≥ 6F (0.070 inches/1.78 mm)	3.50 - 4.00 mm: ≥5F (0.056 inches/1.42 mm) 4.50 - 5.00 mm: ≥6F (0.070 inches/1.78 mm)
Shelf life	24 months			

* The 48 mm length is not available in 2.25 mm, 4.50 mm or 5.00 mm diameters.

** 4.50 mm and 5.00 mm diameter sizes are not available in 8 mm and 38 mm lengths.

A. Device Component Description

The SYNERGY stents are comprised of a Platinum Chromium Alloy (PtCr). The stent component is laser cut into a specific geometric pattern, which consists of serpentine rings connected by links that are highly polished to a uniform rounded surface.

Four separate stent models were designed in specific size ranges. A stent model is defined as a variation of a specific geometry pattern designed for various vessel diameters. The four models are defined below:

- Small Vessel (SV): 2.25 mm, 2.50 mm and 2.75 mm
- Workhorse (WH): 3.00 mm and 3.50 mm
- Large Vessel (LV): 4.00 mm, 4.50 mm and 5.00 mm
- Extra Large Vessel (XLV; SYNERGY MEGATRON only): 3.50 mm, 4.00 mm, 4.50 mm and 5.00 mm

The commercial matrices are shown in Table 2 & Table 3 below.

Table 2: SYNERGY, SYNERGY XD, and SYNERGY SHIELD Product Matrix

Stent Length

		8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm	38 mm	48 mm
	SV	2.25 mm	X	X	X	X	X	X	X	
		2.50 mm	X	X	X	X	X	X	X	X
		2.75 mm	X	X	X	X	X	X	X	X
	W H	3.00 mm	X	X	X	X	X	X	X	X
		3.50 mm	X	X	X	X	X	X	X	X
	LV	4.00 mm	X	X	X	X	X	X	X	X
		4.50 mm		X	X	X	X	X		
		5.00 mm		X	X	X	X	X		

Table 3: SYNERGY MEGATRON U.S. Product Matrix

		Stent Length							
		8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm	
	XL V	3.50 mm	X	X	X	X	X	X	X
		4.00 mm	X	X	X	X	X	X	X
		4.50 mm	X	X	X	X	X	X	X
		5.00 mm	X	X	X	X	X	X	X

B. Drug Component Description

The SYNERGY stent drug matrix is composed of the bioabsorbable polymer poly (D,L- lactide-co-glycolide) (PLGA) and the anti-proliferative drug everolimus. The drug to polymer formulation is 45:55 (w/w).

1. Everolimus

The active pharmaceutical ingredient in the SYNERGY stents is everolimus. The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin, and its chemical structure is provided in Figure 1. The nominal total loaded dose of everolimus and coat weight per nominal stent length/diameter is shown in Table 4.

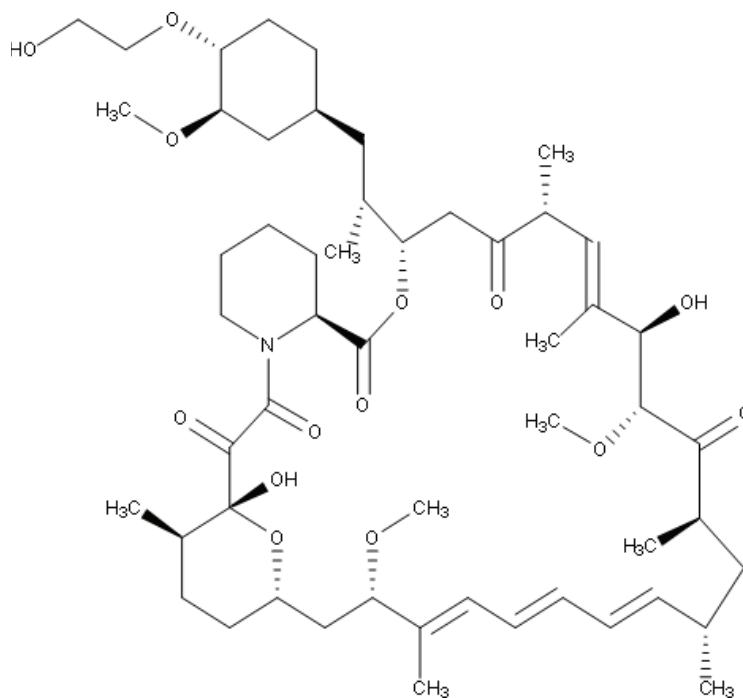


Figure 1: Structure of Everolimus

Table 4: Nominal Loaded Dose of Everolimus (µg) and Coat Weight per Nominal Stent Length and Diameter

		Stent Length								
Design	Stent Model	8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm	38 mm	48 mm
Total Drug Content/ Stent (µg)	SV	38.9	58.3	77.6	96.9	121.1	140.5	159.8	188.9	237.2
	WH	46.5	66.3	92.7	112.5	132.3	158.7	178.5	211.6	271.0
	LV	67.5	96.2	124.8	153.5	182.2	210.8	239.5	287.2	363.6
	XLV	61.5	87.9	123.1	149.5	175.8	211.0	237.4	N/A	N/A
Total Coat Weight/Stent (µg)	SV	87	132	174	218	273	316	360	426	535
	WH	104	149	209	254	298	358	403	477	611
	LV	152	217	281	346	411	475	539	647	819
	XLV	139	198	277	337	396	476	535	N/A	N/A

2. Inactive Ingredient

Polymer—Poly (DL-lactide-co-glycolide) (PLGA)

The SYNERGY stent is abluminally coated with a bioabsorbable coating. The coating consists of bioabsorbable PLGA polymer and everolimus. The PLGA polymer provides controlled and sustained release of available everolimus through the intended time frame, during which the polymer is reabsorbed into the body. The chemical structure of PLGA is shown in Figure 2.

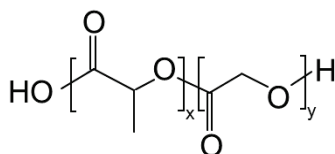


Figure 2: Structure of PLGA

3. Mechanism of Action of Everolimus

At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation in a reversible manner. Everolimus binds to cytosolic FKBP12 and subsequently inhibits activation of the regulatory kinase mTOR (mammalian target of rapamycin).¹ This inhibition results in cell arresting at the late G1 phase in the cell cycle and thereby impedes functions that govern cell metabolism, growth, and proliferation.²

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are alternatives for the improvement of luminal diameter in patients with STEMI. These may include other percutaneous coronary interventions (such as balloon angioplasty and the placement of other stents), and coronary artery bypass graft surgery (CABG). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

US Marketing History

The Original PMA (P150003) for SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail and Over-The-Wire) received approval on October 2, 2015. The manufacture of SYNERGY MR and OTW platforms for distribution in the US has been discontinued.

As of April 24, 2024, approximately 3,608,579 SYNERGY family stents have been distributed in the United States.

International Marketing (OUS) History

SYNERGY MR became available in international markets outside of the US (OUS) in November 2012. As of April 24, 2024, approximately 4,160,229 SYNERGY family stents have been distributed OUS.

Table 5 lists countries where the SYNERGY product is currently commercially available. No products have been withdrawn from the market in any country for any reason.

Table 5: Countries with SYNERGY Commercial Availability

Albania	Algeria	Andorra	Angola
Argentina	Aruba	Australia	Austria
Azerbaijan	Bahamas	Bahrain	Bangladesh
Barbados	Belarus	Belgium	Bermuda
Bolivia	Bonaire & Saba	Bosnia & Herzegovina	Botswana
Botswana	Brazil	Brunei	Bulgaria
Cambodia	Canada	Cayman Islands	Chile
China	Colombia	Costa Rica	Croatia
Curaçao	Cyprus	Czech Republic	Denmark
Dominican Republic	Ecuador	El Salvador	Estonia
Finland	France	Georgia	Germany
Great Britain	Greece	Guatemala	Guyana
Haiti	Hong Kong	Hungary	Iceland
India	Indonesia	Iran	Iraq
Ireland	Israel	Italy	Jamaica
Japan	Jordan	Kazakhstan	Kenya
Kosovo	Kuwait	Latvia	Lebanon
Libya	Liechtenstein	Lithuania	Luxembourg
Macau	Malaysia	Malta	Martinique
Mauritius	Mexico	Mongolia	Montenegro
Morocco	Myanmar	Namibia	Nepal
Netherlands, The	New Zealand	North Macedonia, Republic	Norway
Oman	Pakistan	Palestinian National Auth.	Panama
Paraguay	Peru	Philippines	Poland
Portugal	Qatar	Romania	Russian Federation
Saudi Arabia	Serbia	Singapore	Slovakia
Slovenia	South Africa	South Korea	Spain
Sri Lanka	Sweden	Switzerland	Taiwan
Tajikistan	Thailand	Trinidad & Tobago	Tunisia
Turkey	Uganda	Ukraine	United Arab Emirates
United States	Uzbekistan	Venezuela	Vietnam

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse events (in alphabetical order) which may be associated with the use of a coronary stent in native coronary arteries include but are not limited to:

- Abrupt stent closure
- Allergic reaction to anti-coagulant and/or antiplatelet therapy, contrast medium, or stent materials, including the stent metallic components and polymer coating
- Angina
- Arrhythmias, including ventricular fibrillation, ventricular tachycardia, and heart block
- Cardiogenic shock/pulmonary edema

- Death
- Embolization, (air, tissue or thrombotic material or material from devices(s) used in the procedure) including stent embolization or migration
- Heart failure
- Hemorrhage, which may require transfusion, including bleeding and hematoma
- Hypotension/hypertension
- Infection, local or systemic, including fever and pyrogen reaction
- Myocardial ischemia or infarction
- Pain, chest or access site
- Pericardial effusion or cardiac tamponade
- Renal insufficiency or failure
- Respiratory failure
- Restenosis or aneurysm of stented segment
- Stent deformation, collapse, or fracture
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/transient ischemic attack (TIA)
- Vessel trauma requiring surgical repair or re-intervention, including coronary, femoral or radial artery spasm, dissection, occlusion, perforation, rupture, or pseudoaneurysm

Adverse events associated with daily oral administration of everolimus to organ transplant patients include but are not limited to:

- Abdominal pain (including upper abdominal pain)
- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation
- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dysgeusia
- Dyspepsia
- Dyspnea
- Dysuria
- Dry skin
- Edema (Peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia (may include new onset of diabetes)
- Hyperkalemia
- Hyperlipidemia

- Hypertension
- Hypokalemia
- Hypomagnesemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections)
- Insomnia
- Interaction with strong inhibitors and inducers of CYP3A4
- Leukopenia
- Lymphoma and other malignancies (including skin cancer)
- Male infertility (azospermia and/or oligospermia)
- Mucosal inflammation (including oral ulceration and oral mucositis)
- Nausea
- Neutropenia
- Non-infectious pneumonitis
- Pain; extremity, incision site and procedural, back, chest, musculoskeletal
- Proteinuria
- Pruritus
- Pyrexia
- Rash
- Stomatitis
- Thrombocytopenia
- Thrombotic Microangiopathy (TMA)/Thrombotic thrombocytopenic purpura (TTP)/Hemolytic uremic syndrome (HUS)
- Tremor
- Upper respiratory tract infection
- Urinary tract infection
- Vomiting

There may be other potential adverse events that are unforeseen at this time.

For the specific adverse events that occurred in the CLEAR SYNERGY clinical study, please see Section X: Summary of Primary Clinical Studies, below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSED for the original PMA. Because these previously collected data sufficiently represent the performance of the device for the new indications for use, no new non-clinical testing was conducted.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant leveraged the SYNERGY Stent Registry to establish a reasonable assurance of safety and effectiveness of the SYNERGY family of stents in patients with ST-elevated myocardial infarction (STEMI). The study was conducted in eight countries including Canada, the Czech Republic, North Macedonia, Serbia, Spain, Switzerland, the United Kingdom, and the United States under IDE # G170179. Data from this clinical study was the basis for the PMA supplement approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between March 29, 2018 and August 10, 2020. The database for this Panel Track Supplement reflected data collected through August 10, 2021 and included 730 patients. There were 29 investigational sites.

The SYNERGY Stent Registry was a prospective, multicenter, open label, single-arm study to assess the safety and effectiveness of the SYNERGY family of stents in patients with STEMI. The SYNERGY Stent Registry was embedded in the CLEAR SYNERGY (OASIS 9) clinical study performed by Population Health Research Institute (PHRI).

The primary endpoint for the study was the rate of major adverse cardiac events (MACE) at 1 year. This rate was compared to a historical performance goal of 9.45% derived from previous percutaneous coronary intervention (PCI) STEMI trials.

An event adjudication committee was responsible for adjudicating primary outcome events. Target lesion revascularization (TVR), target vessel revascularization (TVR) and stent thrombosis were adjudicated by a core laboratory. An independent data monitoring committee oversaw the overall safety of patients in the trial by monitoring the conduct of the trial and the integrity of the data in the trial.

Additional Drug Trial

Most (N=533) patients in the SYNERGY Stent Registry study were also enrolled in the larger (N=7,062) CLEAR SYNERGY (OASIS 9) trial. The CLEAR SYNERGY trial was a randomized, placebo-controlled, double-blind, 2x2 factorial study in which patients received daily regimens of any combination of 2 experimental drug therapies or placebo after acute MI. Additional discussion of this unusual aspect of the trial design appears later in this document.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the SYNERGY Stent Registry was limited to patients who met the following inclusion criteria:

- Presenting with STEMI and referred for PCI within 12 hours of symptom onset, had a culprit lesion amenable to stenting, and had planned SYNERGY stent implantation

Patients were not permitted to enroll in the SYNERGY Stent Registry if they met any of the following exclusion criteria:

- Age $\leq$ 18 years

- Pregnancy, breastfeeding, or women of childbearing potential who are not using an effective method of contraception
- Any medical, geographic, or social factor making study participation impractical or precluding required follow-up
- Systolic blood pressure <90 mm Hg
- Active diarrhea
- Known allergy or contraindication to everolimus, the SYNERGY stent or any of its components
- Unable to receive dual antiplatelet therapy
- History of cirrhosis or current severe hepatic disease
- Current or planned use of: cyclosporine, verapamil, HIV protease inhibitors, azole antifungals, or macrolide antibiotics
- Creatinine clearance <30 mL/min/1.73 m²
- Serum Potassium >5.0 meq/L

2. Follow-up Schedule

Patients enrolled only in the SYNERGY Stent Registry (N=200) were scheduled to return for follow-up examinations at 3, 6, and 12 months post-procedure. Patients also enrolled in the 2x2 factorial RCT study (N=533) were scheduled to return for additional follow-up visits at 2, 3, 4, and 5 years or until the common study end date.

Prior to the procedure, patients received an electrocardiogram (ECG), laboratory assessments (serum creatinine, serum potassium, hemoglobin, platelet count, white blood cell count), and coronary blood flow was measured. Post-procedure, the objective parameters measured during the study at 3, 6, and 12 months included the same laboratory assessments conducted at baseline. An ECG was also performed at the 12-month follow up visit. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The primary endpoint, which included components for both safety and effectiveness, is the 1-year rate of MACE defined as a composite of:

- cardiovascular (CV) death
- recurrent myocardial infarction (MI)
- unplanned ischemia-driven target vessel revascularization (TVR).

Recurrent MI was defined as a rise of biochemical markers of myocardial necrosis to greater than twice the upper limit of normal (ULN), with the addition of at least one of the following criteria: i) ischemic symptoms, ii) development of new pathological Q waves (distinct from index event), iii) ECG changes of new ischemia, or iv) pathological evidence of MI. If markers were already elevated and had not reached their peak the further elevation of a marker $\geq 50\%$ of a previous value and $>2X$ ULN was required. If biomarkers were stable or decreasing then a re-elevation of $\geq 20\%$ and $>2X$ ULN was required.

Peri-procedural MI (recurrent MI within 24 hours following PCI) was defined as troponin greater than 5 times the ULN or increased by 50% from values documented to falling and greater than or equal to 5 times ULN in patients with already elevated enzymes, with one of the following: a) symptoms suggestive of myocardial ischemia, or b) new ischemic ECG changes.

Ischemia-driven TVR was defined as any ischemia-driven repeat PCI or CABG surgery of the successfully treated target vessel. A TVR was considered ischemia-driven if the target vessel diameter stenosis was $\geq 50\%$ and any of the following were present: i) a positive functional study corresponding to the area served by the target vessel, ii) ischemic ECG changes at rest in a distribution consistent with the target vessel, iii) ischemic symptoms referable to the target vessel. Additionally, any TVR with a $\geq 70\%$ stenosis was considered ischemia-driven even in the absence of clinical or functional ischemia.

With regards to success/failure criteria, the study was considered a success if the SYNERGY stent met the performance goal for the primary endpoint of MACE at one year.

A one-sided z-test for single proportion was used to test whether the observed MACE rate was less than the pre-specified performance goal. If the upper two-sided 95% confidence interval of the observed rate of MACE at 1 year was less than 9.45%, the performance goal would be met.

The primary analysis set for the primary endpoint was the intent to treat (ITT) population. All patients in which a SYNERGY stent entered the guiding catheter, irrespective of whether the stent was successfully deployed and irrespective of whether they were randomized in the drug portion of the larger CLEAR SYNERGY trial, were analyzed. To ensure drug randomization did not positively influence trial success, the primary endpoint was also analyzed in only those patients receiving no active study drug.

i. Secondary Endpoints

With regards to safety, additional endpoints were measured, including stent thrombosis per Academic Research Consortium (ARC) definitions, all-cause death, peri-procedural MI, recurrent MI related to the target vessel (TV-MI), and bleeding per Bleeding Academic Research Consortium (BARC) definitions.

With regards to effectiveness, additional endpoints were measured, including unplanned ischemia-driven target lesion revascularization (TLR) and technical success.

B. Accountability of PMA Cohort

At the time of database lock, of 733 patients enrolled in the PMA study, 99.6% (730) are available for analysis at the completion of the study, the 1 year post-procedure visit. The three patients not evaluable for analysis withdrew their consent.

Table 6: Subject Disposition

	Overall
Enrolled	733
Death with no 1-Year Follow-up Performed	23 (3.1%)
Eligible for 1-Year Follow-up	710
1-Year Follow-up Performed	707 (99.6%)
No 1-Year Follow-up Performed	3 (0.4%)
1-Year Follow-up or Death	730 (99.6%)

Numbers presented as N (%) (count/sample size)

As stated, patients in the analysis set used to support PMA approval were enrolled in either the SYNERGY Stent Registry only, or the SYNERGY Stent Registry and a 2x2 factorial randomized drug study. All patients were assigned to be treated with a SYNERGY stent. Patients randomized in the drug study were assigned to receive either active drug 1 + active drug 2, active drug 1 + drug 2 placebo, drug 1 placebo + active drug 2, or drug 1 placebo + drug 2 placebo. As the drugs were not being evaluated in this review, the 4 drug study groups were combined for FDA analysis into 2 groups – patients who were randomized to any active study drug, and patients who were randomized to both study drugs’ placebos. Table 7 shows the distribution of study participants by treatment group.

Table 7: Treatment Assignment

	Number Enrolled
SYNERGY Stent Registry Only	200 (27%)
Stent Registry and Randomized to Drug Study	533 (73%)
Randomized to Active Study Drug	408 (56%)
Randomized to Study Drug Placebo	125 (17%)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are provided in Table 8 below. The mean age was 60.2 years and 76% of patients were male. Patients were predominantly white (91.8%) and mildly overweight (body mass index (BMI) 28.4).

The age and sex of the patients enrolled are approximately representative of patients hospitalized with STEMI in the US. However, the race and ethnicity of study patients are not representative of US STEMI patients. Research suggests approximately 65% of patients

hospitalized for STEMI in the US are white, while approximately 12% are Black or African American and 17% are Hispanic or Latino. It is still reasonable to consider the results of the study to be applicable for all patients who might be treated by the SYNERGY stent because previous drug eluting stent studies have shown similar 1-year MACE rates across race and ethnicity after PCI.

Table 8: Demographics

Demographics	SYNERGY (N=733)
Age (years)	60.2±10.6
Sex	
Male	75.9% (557)
Female	24.0% (176)
Race	
American Indian or Alaskan Native	0.1% (1)
Asian	0.4% (3)
Black or African American	1.2% (9)
Native Hawaiian or Other Pacific Islander	0.1% (1)
White	91.8% (673)
Other	5.6% (41)
Unknown	0.7% (5)
Ethnicity	
Hispanic or Latino	2.7% (20/733)
Not Hispanic or Latino	97.3% (713/733)
Height (cm)	172.5±9.4
Weight (kg)	84.8±17.5
BMI (kg/m ²)	28.4±5.1
% (N), mean±standard deviation	

Table 9 shows the baseline clinical characteristics and medical history of the enrolled STEMI patients. Nineteen percent of patients had diabetes, 7.1% had a prior MI, 2% had previous

heart failure and nearly 41% were current smokers. Almost half were found to have multi-vessel coronary artery disease at the time of the index procedure.

Table 9: Baseline Clinical Characteristics

Baseline Characteristics	SYNERGY (N=733)
At Presentation to Hospital	
Location of MI	
Inferior	52.4% (384)
Anterior	41.3% (303)
Lateral	11.2% (82)
Posterior	6.5% (48)
Heart Failure at Presentation	7.8% (57)
Cardiovascular History	
Previous MI	7.1% (52)
Previous PCI	8.3% (61)
Previous CABG	1.9% (14)
Previous Heart Failure	2.0% (15)
New York Heart Association (NYHA) Class I	0.4% (3)
NYHA Class II	0.5% (4)
NYHA Class III	0.7% (5)
NYHA Class IV	0.4% (3)
Previous Stroke	1.2% (9)
Previous TIA	1.0% (7)
Peripheral Arterial Disease	1.8% (13)
Atrial Fibrillation/Atrial Flutter	2.5% (18)
Other Relevant Characteristics	
Multi-Vessel Disease	47.7% (350)
Hypertension	47.9% (351)
Hyperlipidemia	34.0% (249)

Baseline Characteristics	SYNERGY (N=733)
Diabetes	19.4% (142)
Insulin treated	4.4% (32)
Not insulin treated	14.9% (109)
History of Smoking	53.9% (395)
Current Smoker	40.9% (300)
Previous Smoker	13.0% (95)
History of Cancer	5.9% (43)
Previous use of oral anticoagulant	1.9% (14)

Key Baseline Vessel Characteristics: Most patients (75%) had one culprit lesion treated in the target vessel. Target vessels were most commonly the left anterior descending (LAD) and right coronary arteries (RCA). The majority of patients had thrombolysis in myocardial infarction (TIMI) 0 flow (no flow) in the target vessel pre-PCI (67.4%). Additional baseline vessel characteristics can be found in Table 10.

Table 10: Baseline Vessel Characteristics

Characteristics	Target Vessels (N=939)
LAD	43.1% (405/939)
Circumflex	13.1% (123/939)
RCA	43.2% (406/939)
Left Main	0.3% (3/939)
CABG Graft	0.2% (2/939)
TIMI Flow in Target Vessel	
0	67.4% (494/733)
3	8.9% (65/733)
Patients with 1 Treated Lesion	75.3% (552/733)
Patients with 2 or more Treated Lesions	24.7% (181/733)

A small percentage (5%) of patients had lesions in non-target vessels that were treated during the index procedure. Of those, 86% were treated with a SYNERGY stent. Some patients (13%) went on to have additional procedures to treat lesions outside of the target vessel at a later date (staged procedures).

Key Procedural Characteristics: The average time from symptom onset to hospital arrival was nearly three hours, and the average time from hospital arrival to PCI was under two hours. Over 90% of access sites were radial, and thrombectomy use was uncommon (less than 10%). Patients were treated with an average of 1.3 stents (955 SYNERGY stents, 27 non-SYNERGY stents), and 97.5% of subjects had TIMI 3 Flow post-PCI procedure. Unfractionated heparin was the most common anticoagulant given during the index PCI (99.7%). Additional procedural characteristics are shown in Table 11.

Table 11: Procedural Characteristics

Procedure Data	SYNERGY Stent Registry
Presentation and Hospitalization Characteristics	
Time from symptom onset to hospital arrival (minutes)	168.5±214.7
Time from hospital arrival to procedure (minutes)	104.3±155.3
Length of Hospital Stay (days)	3.4±3.5
Characteristics of Devices Used During Procedure	
Devices Used to Treat Target Lesions	939
SYNERGY Stent	97.8% (918/939)
Non-SYNERGY Stent	1.4% (13/939)
Angioplasty Balloon	0.9% (8/939)
Total Stents Implanted (Target and Non-Target Lesions)	982
SYNERGY Stents	97.2% (955/982)
Non-SYNERGY Stents	2.7% (27/982)
Number of Stents Implanted per Patient	1.3±0.6*
Stent Diameter of SYNERGY Stents (mm)	4.0±1.8*
Stent Diameter of Non-SYNERGY Stents (mm)	3.1±0.6*
Total Stent Length per Patient (mm)	24.3±7.6*
Thrombectomy Use	9.5% (70/733)
Intra-Aortic Balloon Pump (IABP) Use	0.8% (6/733)
Procedure Characteristics	
Radial Access	90.3% (662/733)
TIMI 3 Flow post-PCI	97.5% (715)

*Mean ± standard deviation

Medication Usage: Approximately 20% of patients had a prior aspirin regimen, and 3.4% had a prior dual antiplatelet therapy (DAPT; aspirin plus a P2Y12 inhibitor) regimen. Nearly all patients were prescribed DAPT at discharge, and 67% continued to be on DAPT at 12 months after the procedure. Other medication information is shown in Table 12.

Table 12: Medication to 12 Months

Medication	SYNERGY Stent Registry (N=733)
Prior Antiplatelet Regimens	
Aspirin	19.5% (143)
P2Y12 Inhibitor	3.7% (27)
DAPT	3.4% (25)
Medication Use During PCI	
Unfractionated Heparin	99.7% (731)
Bivalirudin	0.3% (2)
Enoxaparin	0.4% (3)
GP IIb IIIa Inhibitor	14.6% (107)
Cangrelor	0.5% (4)
Medication at Discharge	
Beta Blocker	70.4% (516)
ACEI or ARB	74.5% (546)
Statin	94.0% (689)
Anticoagulant	16.1% (118)
Aspirin	97.4% (714)
P2Y12 Inhibitor	97.7% (716)
DAPT	95.9% (703)
Antiplatelet Therapy at 3 Months	
Aspirin	89.4% (655)
P2Y12 Inhibitor	91.0% (667)
DAPT	87.9% (644)
Antiplatelet Therapy at 6 Months	
Aspirin	86.6% (635)
P2Y12 Inhibitor	89.2% (654)
DAPT	84.3% (618)
Antiplatelet Therapy at 12 Months	
Aspirin	85.4% (626)
P2Y12 Inhibitor	71.8% (526)

Medication	SYNERGY Stent Registry (N=733)
DAPT	67.3% (493)

D. Safety and Effectiveness Results

The incidence of the primary endpoint in the ITT population, the composite of CV death, recurrent MI, and unplanned ischemia driven target vessel revascularization (MACE) at 12 months, was 4.8% [CI 3.4, 6.6]. The prespecified performance goal was 9.45%. Statistical conclusions cannot be drawn due to the unknown poolability of the results from groups assigned to varying experimental drug regimens in the CLEAR SYNERGY study. However, the data demonstrate that each group, regardless of treatment assignment, had MACE rates well below the performance goal, making it reasonable to interpret the trial as a success. Table 13 presents the primary endpoint results for the ITT population as well as for patients not enrolled in the drug study, patients enrolled in the drug study who received only placebos, and for patients enrolled in the drug study who received any active drug.

Table 13: Primary Endpoint Results

SYNERGY Stent Registry	MACE at 1 Year (Event Rate, 95% CI)
ITT Population	(35/730) 4.8% [3.4, 6.6]
Registry and Placebo (No Drug Treatment)	(18/322) 5.5% [3.4, 8.7]
Randomized to Active Drug	(17/408) 4.2% [2.5, 6.6]

1. Safety Results

The primary analysis of safety, which was a component of the primary endpoint, was based on the ITT cohort of 730 patients available for the 12-month evaluation as described above. Additional key safety outcomes for this study, including components of the primary endpoint, are presented below in Table 14. Adverse events are reported in Table 15.

Definite or probable stent thrombosis was identified by the applicant as a key secondary endpoint and was rare, occurring in 1.2% of patients.

Table 14: Summary of Safety Outcomes

Event	SYNERGY Stent Registry
In Hospital	
Death	0.4% (3/733)
Cardiac Death	0.4% (3/733)
Peri-Procedural Recurrent MI	0.5% (4/733)
Related to Target Vessel	0.3% (2/733)
Not Related to Target Vessel	0.3% (2/733)
At 1 Year	

Death	3.1% (23/730)
Cardiac Death	2.6% (19/730)
Non-Cardiac Death	0.5% (4/730)
Recurrent MI	2.1% (15/730)
Related to Target Vessel	1.1% (8/730)
Not Related to Target Vessel	1.0% (7/730)
Stent Thrombosis (Definite or Probable)	1.2% (9/730)
Acute (0-24 Hours)	0.3% (2/730)
Subacute (24 Hours-30 Days)	0.7% (5/730)
Late (30 Days-1 Year)	0.3% (2/730)
Bleeding (BARC 2-5)	2.5% (18/730)
BARC 2	2.2% (16/730)
BARC 3-5	0.3% (2/730)

Adverse effects that occurred in the PMA clinical study:

Adverse events associated with the use of the SYNERGY family of stents have been previously characterized in the EVOLVE II study used to support the original PMA approval. Serious adverse events (SAEs) occurred in 49 patients in the SYNERGY Stent Registry study of patients with STEMI. Acute kidney injury was reported in five patients and was the most common SAE. This event is a known risk of the PCI procedure. The frequency and nature of SAEs observed in the SYNERGY Stent Registry are similar to those observed in previous clinical trials of coronary interventional devices.

Table 15: Serious Adverse Events

System Organ Class	Events Reported	Percentage of Patients with Event
Blood and Lymphatic System Disorders	Anemia (1), splenic infarction (1)	0.3% (2/730)
Cardiac Disorders	Acute myocardial infarction (2), unstable angina (1), myocardial ischemia (1), palpitations (1), ventricular tachycardia (2)	1.0% (7/730)
Gastrointestinal Disorders	Abdominal pain (2), colitis	1.4% (10/730)

System Organ Class	Events Reported	Percentage of Patients with Event
	(2), constipation (1), ileus (1), melena (1), pancreatitis (2), rectal hemorrhage (1), small intestinal obstruction (1)	
General Disorders and Administration Site Conditions	Asthenia (1), chest pain (2), non-cardiac chest pain (1)	0.5% (4/730)
Hepatobiliary Disorders	Acute cholecystitis (1)	0.1% (1/730)
Immune System Disorders	Drug hypersensitivity (1)	0.1% (1/730)
Infections and Infestations	Appendicitis (1), viral gastroenteritis (1), pneumonia (3), respiratory tract infection (1)	0.7% (5/730)
Injury, Poisoning and Procedural Complications	Femur fracture (1), hip fracture (1), splenic rupture (1), subdural hematoma (1), traumatic hematoma (1)	0.7% (5/730)
Investigations	Hemoglobin decreased (1)	0.1% (1/730)
Metabolism and Nutrition Disorders	Ketoacidosis (1), lactic acidosis (1)	0.3% (2/730)
Musculoskeletal and Connective	Arthralgia (1), groin pain (1),	0.4% (3/730)

System Organ Class	Events Reported	Percentage of Patients with Event
Tissue Disorders	pain in extremity (1)	
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	Bladder neoplasm (1), brain neoplasm (1), paraganglion neoplasm (1)	0.4% (3/730)
Nervous System Disorders	Depressed level of consciousness (1), dizziness (1), syncope (2), vascular dementia (1)	0.7% (5/730)
Psychiatric Disorders	Delirium (1)	0.1% (1/730)
Renal and Urinary Disorders	Renal infarct (1), urinary retention (1), acute kidney injury (5)	1% (7/730)
Respiratory, Thoracic and Mediastinal Disorders	Acute respiratory failure (2), chronic obstructive pulmonary disease (4), hypoxia (1), pulmonary hypertension (1), respiratory failure (1)	0.8% (6/730)
Skin and Subcutaneous Tissue Disorders	Decubitus ulcer (1), Stevens-Johnson syndrome (1)	0.3% (2/730)
Surgical and Medical Procedures	Craniotomy (1), hysterectomy (1)	0.3% (2/730)

System Organ Class	Events Reported	Percentage of Patients with Event
Vascular Disorders	Hematoma (1), hemorrhagic shock (1), deep vein thrombosis (1), hypertensive urgency (2)	0.7% (5/730)

2. Effectiveness Results

The primary analysis of effectiveness, which was a component of the primary endpoint, was based on the ITT cohort of 730 evaluable patients at the 12-month time point as described above. Additional key effectiveness outcomes, including components of the primary endpoint and procedural endpoints, are presented in Table 16.

Technical success, which was defined as successful delivery of the stent with a resulting TIMI flow of 3 and $\leq 50\%$ residual stenosis, was achieved for 97.5% of SYNERGY stents attempted to be delivered. Rates of unplanned target vessel and target lesion revascularization were low.

Table 16: Summary of Effectiveness Outcomes

Event	SYNERGY Stent Registry
In Hospital	
Technical Success (per stent)	97.5% (931/955)
Technical Failure (per stent)	2.5% (24/955)
Failure to Cross/Dilate	0.7% (7/955)
TIMI Flow <3 or ≥50% Residual Stenosis	1.8% (17/955)
Unplanned Target Vessel Revascularization	0.3% (2/733)
Unplanned Target Lesion Revascularization	0.3% (2/733)
At 1 Year	
Unplanned Target Vessel Revascularization	1.0% (7/730)
TVR, PCI	1.0% (7/730)
TVR, CABG	0.0% (0/730)
Unplanned Target Lesion Revascularization	0.8% (6/730)

Long Term Follow-up Outcomes

Stent Registry patients who also participated in the CLEAR SYNERGY RCT study were followed beyond 1 year for a maximum of 5 years or through the common study end date, whichever occurred first, according to the study protocol. Table 17 provides the outcomes for those patients for years 2 through 5.

Table 17: SYNERGY Stent Registry Clinical Outcomes through 5-Years

	2-Year	3-Year	4-Year	5-Year
EFFICACY				
Unplanned TVR, Overall	2.2% (16/730)	2.7% (20/730)	3.0% (22/730)	3.2% (23/730)
Unplanned TLR, Overall	1.9% (14/730)	2.5% (18/730)	2.6% (19/730)	2.7% (20/730)
TLR, PCI	1.8% (13/730)	2.2% (16/730)	2.3% (17/730)	2.5% (18/730)
TLR, CABG	0.1% (1/730)	0.3% (2/730)	0.3% (2/730)	0.3% (2/730)
Unplanned Non-TLR, Overall	0.4% (3/730)	0.4% (3/730)	0.5% (4/730)	0.5% (4/730)
Non-TLR, PCI	0.4% (3/730)	0.4% (3/730)	0.4% (3/730)	0.4% (3/730)
Non-TLR, CABG	0.0% (0/730)	0.0% (0/730)	0.1% (1/730)	0.1% (1/730)
SAFETY				
MACE	6.7% (49/730)	7.9% (58/730)	8.6% (63/730)	9.0% (66/730)
Total Death	3.8% (28/730)	4.5% (33/730)	5.2% (38/730)	5.3% (39/730)

Cardiac Death	3.3% (24/730)	3.7% (27/730)	3.8% (28/730)	4.0% (29/730)
Non-Cardiac Death	0.5% (4/730)	0.8% (6/730)	1.4% (10/730)	1.4% (10/730)
Recurrent MI	2.7% (20/730)	3.3% (24/730)	3.8% (28/730)	4.1% (30/730)
Related to Target Vessel	1.5% (11/730)	1.8% (13/730)	2.1% (15/730)	2.1% (15/730)
Not Related to Target Vessel	1.2% (9/730)	1.5% (11/730)	1.8% (13/730)	2.1% (15/730)
ARC Stent Thrombosis	1.5% (11/730)	1.8% (13/730)	1.9% (14/730)	2.2% (16/730)
Definite or Probable	1.5% (11/730)	1.8% (13/730)	1.9% (14/730)	2.2% (16/730)
Definite	1.2% (9/730)	1.5% (11/730)	1.6% (12/730)	1.9% (14/730)
Probable	0.3% (2/730)	0.3% (2/730)	0.3% (2/730)	0.3% (2/730)
Numbers presented as N (%) (count/sample size) Abbreviations: MI=myocardial infarction, TLR=target lesion revascularization, TVR=target vessel revascularization, MACE=major adverse cardiac event				

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: sex, age, and diabetic status.

The study was not specifically powered for these subgroups.

Results by Sex:

The MACE primary endpoint and its components were evaluated by sex. Female patients experienced numerically higher rates of cardiac death and recurrent MI than male patients. This finding is consistent with prior research demonstrating poorer outcomes after STEMI in female patients compared with male patients, which is multi-factorial and is unlikely to be related to the SYNERGY stent.

Table 18: Outcomes at 1 Year by Sex

Outcomes	SYNERGY Stent Female Patients (N=176)	SYNERGY Stent Male Patients (N=554)
MACE	6.3% (11)	4.3% (24)
Cardiac Death	4.0% (7)	2.2% (12)
Recurrent MI	2.8% (5)	1.8% (10)
MI Related to TV	1.7% (3)	0.9% (5)
Unplanned Target Vessel Revascularization	0.6% (1)	1.1% (6)

Results by Age:

Of the 733 patients enrolled in the CLEAR SYNERGY Stent Registry analysis set, 258 were 65-years old or older at enrollment (35.2%). Outcomes for patients 65-years old or older at enrollment versus patients younger than 65 years old at enrollment are shown in Table 19. Although intended to be exploratory only, outcome rates were higher for all endpoints in those 65 years old or older at enrollment compared to those younger than 65 years old (MACE Rate: 7.4% vs. 3.4%).

Table 19: Outcomes at 1 Year by Age

Outcomes	≥ 65 Years Old (N=257)	< 65 Years Old (N=473)
MACE	7.4% (19)	3.4% (16)
Cardiac Death	3.9% (10)	1.9% (9)
Recurrent MI	3.1% (8)	1.5% (7)
MI Related to TV	2.3% (6)	0.4% (2)
Unplanned Target Lesion Revascularization	1.2% (3)	0.6% (3)

Results by Diabetic Status:

There were 142 subjects enrolled in the CLEAR SYNERGY Stent Registry analysis set who had diabetes (medically-treated or otherwise) at baseline (19.4%). Primary endpoints for diabetic vs. non-diabetic subjects are shown in Table 20. Although these results were intended to be exploratory only, outcome rates were higher for all endpoints in subjects with diabetes at baseline vs. those without (MACE Rate: 9.2% vs. 3.7%). This is consistent with prior research showing poorer outcomes after STEMI in patients with diabetes compared to patients without diabetes and is unlikely to be related to the SYNERGY stent.

Table 20: Outcomes at 1 Year by Diabetic Status

Outcomes	Patients with Diabetes (N=142)	Patients without Diabetes (N=588)
MACE	9.2% (13)	3.7% (22)

Outcomes	Patients with Diabetes (N=142)	Patients without Diabetes (N=588)
Cardiac Death	6.3% (9)	1.7% (10)
Recurrent MI	2.1% (3)	2.0% (12)
MI Related to TV	1.4% (2)	1.0% (6)
Unplanned Target Lesion Revascularization	1.4% (2)	0.7% (4)

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 35 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The SYNERGY Stent Registry was a prospective, multicenter, open label, single-arm study of the use of the SYNERGY stent in patients with ST-elevated myocardial infarction. The

SYNERGY stent successfully crossed the lesion and assisted in restoring TIMI 3 flow in 97.5% of patients. The rates of unplanned, ischemia-driven TVR (1.0%) and TLR (0.8%) remained low through 1 year of follow up, indicating that nearly all (99%) treated vessels remained patent for at least 1 year after implantation of the SYNERGY stent. The MACE rate for patients treated with the stent was 4.8% [CI 3.4, 6.6], lower than the performance goal of 9.45%. Together, this evidence demonstrates a reasonable assurance that the SYNERGY stent is effective for improving luminal diameter in patients with STEMI.

B. Safety Conclusions

The risks of the device are based on previous nonclinical laboratory and animal studies as well as data collected in previous clinical studies to support original PMA approval and subsequent expansions of the indications for use. The current clinical study conducted to support PMA supplement approval as described above contributed additional information about the risks associated with the SYNERGY stent when used to treat patients with STEMI.

In the SYNERGY Stent Registry, a total of 10 patients (1.2%) experienced definite or probable stent thrombosis, with associated mortality in 5 patients (0.6%). The overall death rate at 1 year was 3.1%, the cardiac death rate was 2.6%, and the recurrent MI rate was 2.0%.

Together, this evidence demonstrates a reasonable assurance that the SYNERGY stent is safe when used to improve luminal diameter in patients with STEMI.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA supplement approval as described above. STEMI is a life-threatening event, and restoring blood flow to the target vessel is critical. At the time of treatment, 67% of patients had no flow through the target lesion, and nearly all had flow restored after the PCI procedure and placement of the SYNERGY stent. This benefit was sustained to at least one year, as demonstrated by the low number of revascularization procedures in the target vessel.

The probable risks of the device when used for this indication are also based on data collected in a clinical study conducted to support PMA approval as described above. Stent thrombosis is the most serious risk directly attributable to the device itself (rather than the procedure, index STEMI, or underlying disease state), and patients with acute coronary syndromes such as STEMI are known to have a higher risk of stent thrombosis than patients with stable ischemic disease. The observed rate of definite or probable stent thrombosis in the study (1.2%) was low, with most events taking place within 24 hours to 30 days of the index procedure.

Additional factors considered in determining probable risks and benefits for the Synergy stent included:

1. The study design was unconventional. The 2x2 factorial drug study that 73% of the Synergy Stent Registry patients also participated in could have confounded the results. However, the study results demonstrate that the outcomes in patients that did not receive any active experimental drugs were still below the performance goal, even with the larger confidence interval created by the decreased sample size.

2. The study was a single arm design. There are no currently marketed drug eluting stents in the US indicated for patients with STEMI. However, randomizing STEMI patients to anything other than a drug eluting stent would be infeasible, as DES are the current standard of care and used in the overwhelming majority of patients. Therefore, using a performance goal derived from previous PCI STEMI studies was reasonable.

1. Patient Perspective

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for patients with ST-elevated myocardial infarction the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on January 27, 2025. The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI.

REFERENCES

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2. Grube E, Buellesfeld L. Rapamycin analogs for stent-based local drug delivery. Everolimus- and tacrolimus-eluting stents. *Herz*. Mar 2004;29(2):162-6.
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